

### **REMARKS**

Claims 1-6, 8, 10, 11, 36-47, 54 and 57 were pending in the application. Claims 2-6, 8, 10 and 11 have been cancelled without prejudice, claims 1, 37, 54 and 57 have been amended and new claims 58-64 have been added. Therefore, claims 1, 37-47, 54 and 57-64 are currently pending.

No new matter has been added. Support for the amendments to claim 1 may be found, for example, at least at page 9, lines 8-22 and page 14, lines 11 through page 15, line 20 of the specification as originally filed. Claim 37 was amended to provide proper dependencies. Support for the amendments to claim 54 may be found, for example, at least in Table 2, at pages 17-45 of the specification as originally filed. Support for the amendments to claim 57 may be found, for example, at least at page 101, line 10 through page 102, line 9 of the specification as originally filed. Support for new claim 58 may be found, for example, at least in original claim 6 and at page 6, line 24 through page 7, line 20 of the specification as originally filed. Support for new claims 59 and 60 may be found, for example, at least at page 3, lines 9-11 of the specification as originally filed. Support for new claim 61 may be found, for example, at least at page 6, line 24 through page 7, line 20 of the specification as originally filed. Support for new claim 62 may be found, for example, at least at page 10, lines 12-20 of the specification as originally filed. Support for new claim 63 may be found, for example, at least at page 8, line 32 through page 9, line 22 of the specification as originally filed. Support for new claim 64 may be found, for example, at least at page 6, line 24 through page 7, line 20 of the specification as originally filed.

Cancellation of and/or amendments to the claims should in no way be construed as an acquiescence to any of the Examiner's objections or rejections. Cancellation of and/or amendments to the claims is being made solely to expedite prosecution of the above-identified application. Applicants reserve the option to further prosecute the same or similar claims in the present or another patent application. Cancellation of and/or amendments to the claims is not related to any issues of patentability.

Without acquiescing to the accuracy of the Examiner's characterization of the claims at paragraphs 9 and 13 of the present Office Action, Applicants respectfully submit that the inventions described in U.S. Patent Nos. 6,500,812; 6,624,168; 6,642,270; 6,683,068; 6,818,634; 6,818,635; 6,833,365; 6,846,939; 6,849,615; 7,045,507 and 7,094,806 and U.S. Patent Application Nos. 10/692,563; 10/752,378, 10/786,881 and 10/943,571 and the present application were commonly owned at the time the invention in this application was made, as evidenced by copies of the assignments submitted herewith at Appendices A-O, respectively.

***Rejection of Claims 1, 8, 11 and 36-47 on the Ground of Nonstatutory Obviousness-type Double Patenting***

Claims 1, 8, 11 and 36-47 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims in each of U.S. Patent Nos. 6,500,812; 6,624,168; 6,642,270; 6,683,068; 6,818,634; 6,818,635; 6,833,365; 6,846,939; 6,849,615; 7,045,507 and 7,094,806. Specifically, the Examiner asserts that “[a]lthough the conflicting claims are not identical, they are not patentable distinct from each other because the instant claims represent a genus over claims in each of U.S. Patent Nos. 6,500,812; 6,624,168; 6,642,270; 6,683,068; 6,818,634; 6,818,635; 6,833,365; 6,846,939; 6,849,615; 7,045,507; 7,094,806 and 7,202,235.” The Examiner also asserts that the above-listed patents “recite methods of treating a subject with a bacterial, fungal or tetracycline responsive states, an effective amount of tetracycline compounds and their derivatives” and that these patents also “teach the treatment of mammals including humans.” The Examiner further asserts that “a method of treating a DMTR would include a method of treating a bacterial infection, a fungal infection or a tetracycline response (*sic*) using an effective amount of tetracyclines.”

Applicants respectfully traverse this rejection as set forth below.

***U.S. Patent No. 6,500,812***

Claims 1, 8, 11 and 36-47 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 14 and 15 of U.S. Patent No. 6,500,812 (hereinafter “the ‘812 patent”).

With regard to claims 8 and 11, Applicants respectfully submit that this rejection is moot in view of the cancellation of these claims. With regard to claims 1 and 36-47, Applicants respectfully traverse.

As amended, claims 1 and 36-47 are ***directed to methods for treating a DMTR associated with splicing in a subject*** by administering to the subject an effective amount of a substituted tetracycline compound of formula I.

In contrast, claims 14 and 15 of the ‘812 patent are ***directed to methods for treating a tetracycline responsive state*** in a mammal by administering to the mammal a 13-substituted methacycline compound.

Applicants respectfully submit that claims 14 and 15 of the ‘812 patent fail to teach or suggest the currently claimed methods of treating a DMTR associated with splicing in a subject by administering a substituted tetracycline compound of formula (I). Moreover one of skill in the art

would not be motivated by the claims in the '812 patent to develop methods of treating a DMTR associated with splicing in a subject by administering a substituted tetracycline compound. Accordingly, claims 1 and 36-47 are not obvious in view of claims 14 and 15 of the '812 patent, and therefore, Applicants respectfully request reconsideration and withdrawal of this rejection.

*U.S. Patent No. 6,624,168*

Claims 1, 8, 11 and 36-47 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 6-11 of U.S. Patent No. 6,624,168 (hereinafter "the '168 patent").

With regard to claims 8 and 11, Applicants respectfully submit that this rejection is moot in view of the cancellation of these claims. With regard to claims 1 and 36-47, Applicants respectfully traverse.

As amended, claims 1 and 36-47 are ***directed to methods for treating a DMTR associated with splicing in a subject*** by administering to the subject an effective amount of a substituted tetracycline compound of formula I.

In contrast, claims 6-11 of the '168 patent are ***directed to methods of treating a tetracycline responsive state (e.g., a bacterial infection associated with E. coli, S. aureus or E. faecalis)*** in a mammal by administering to the mammal a 7, 8 and 9-substituted tetracycline compound.

Applicants respectfully submit that claims 6-11 of the '168 patent fail to teach or suggest the currently claimed methods of treating a DMTR associated with splicing in a subject by administering a substituted tetracycline compound of formula (I). Moreover one of skill in the art would not be motivated by the claims in the '168 patent to develop methods of treating a DMTR associated with splicing in a subject by administering a substituted tetracycline compound. Accordingly, claims 1 and 36-47 are not obvious in view of claims 6-11 of the '168 patent, and therefore, Applicants respectfully request reconsideration and withdrawal of this rejection.

*U.S. Patent No. 6,642,270*

Claims 1, 8, 11 and 36-47 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 6-14 of U.S. Patent No. 6,642,270 (hereinafter "the '270 patent").

With regard to claims 8 and 11, Applicants respectfully submit that this rejection is moot in view of the cancellation of these claims. With regard to claims 1 and 36-47, Applicants respectfully traverse.

As amended, claims 1 and 36-47 are ***directed to methods for treating a DMTR associated with splicing in a subject*** by administering to the subject an effective amount of a substituted tetracycline compound of formula I.

In contrast, claims 6-14 of the '270 patent are ***directed to methods of treating a tetracycline responsive state (e.g., a bacterial infection associated with E. coli, S. aureus or E. faecalis)*** in a mammal by administering to the mammal a 7-substituted fused ring tetracycline compound.

Applicants respectfully submit that claims 6-14 of the '270 patent fail to teach or suggest the currently claimed methods of treating a DMTR associated with splicing in a subject by administering a substituted tetracycline compound of formula (I). Moreover one of skill in the art would not be motivated by the claims in the '270 patent to develop methods of treating a DMTR associated with splicing in a subject by administering a substituted tetracycline compound. Accordingly, claims 1 and 36-47 are not obvious in view of claims 6-14 of the '270 patent, and therefore, Applicants respectfully request reconsideration and withdrawal of this rejection.

*U.S. Patent No. 6,683,068*

Claims 1, 8, 11 and 36-47 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 17-21 of U.S. Patent No. 6,683,068 (hereinafter "the '068 patent").

With regard to claims 8 and 11, Applicants respectfully submit that this rejection is moot in view of the cancellation of these claims. With regard to claims 1 and 36-47, Applicants respectfully traverse.

As amended, claims 1 and 36-47 are ***directed to methods for treating a DMTR associated with splicing in a subject*** by administering to the subject an effective amount of a substituted tetracycline compound of formula I.

In contrast, claims 17-21 of the '068 patent are ***directed to methods of treating a tetracycline responsive state (e.g., a bacterial infection associated with E. coli, S. aureus or E. faecalis)*** in a subject by administering to the subject a 7,9-substituted tetracycline compound.

Applicants respectfully submit that claims 17-21 of the '068 patent fail to teach or suggest the currently claimed methods of treating a DMTR associated with splicing in a subject by administering a substituted tetracycline compound of formula (I). Moreover one of skill in the art would not be motivated by the claims in the '068 patent to develop methods of treating a DMTR associated with splicing in a subject by administering a substituted tetracycline compound.

Accordingly, claims 1 and 36-47 are not obvious in view of claims 17-21 of the '068 patent, and therefore, Applicants respectfully request reconsideration and withdrawal of this rejection.

*U.S. Patent No. 6,818,634*

Claims 1, 8, 11 and 36-47 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 27-29 of U.S. Patent No. 6,818,634 (hereinafter "the '634 patent").

With regard to claims 8 and 11, Applicants respectfully submit that this rejection is moot in view of the cancellation of these claims. With regard to claims 1 and 36-47, Applicants respectfully traverse.

As amended, claims 1 and 36-47 are ***directed to methods for treating a DMTR associated with splicing in a subject*** by administering to the subject an effective amount of a substituted tetracycline compound of formula I.

In contrast, claims 27-29 of the '634 patent are ***directed to methods of treating a tetracycline responsive state (e.g., a bacterial infection associated with E. coli, S. aureus, E. faecalis or E. hirae)*** in a subject by administering to the subject a 7-hydrogen, dialkylamino or heteroaryl-amino substituted tetracycline compound.

Applicants respectfully submit that claims 27-29 of the '634 patent fail to teach or suggest the currently claimed methods of treating a DMTR associated with splicing in a subject by administering a substituted tetracycline compound of formula (I). Moreover one of skill in the art would not be motivated by the claims in the '634 patent to develop methods of treating a DMTR associated with splicing in a subject by administering a substituted tetracycline compound. Accordingly, claims 1 and 36-47 are not obvious in view of claims 27-29 of the '634 patent, and therefore, Applicants respectfully request reconsideration and withdrawal of this rejection.

*U.S. Patent No. 6,818,635*

Claims 1, 8, 11 and 36-47 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 23-26 of U.S. Patent No. 6,818,635 (hereinafter "the '635 patent").

With regard to claims 8 and 11, Applicants respectfully submit that this rejection is moot in view of the cancellation of these claims. With regard to claims 1 and 36-47, Applicants respectfully traverse.

As amended, claims 1 and 36-47 are ***directed to methods for treating a DMTR associated with splicing in a subject*** by administering to the subject an effective amount of a substituted tetracycline compound of formula I.

In contrast, claims 23-26 of the '635 patent are ***directed to methods of treating a tetracycline responsive state (e.g., a bacterial infection associated with E. coli, S. aureus or E. faecalis)*** in a subject by administering to the subject a 7-alkynyl substituted tetracycline.

Applicants respectfully submit that claims 23-26 of the '635 patent fail to teach or suggest the currently claimed methods of treating a DMTR associated with splicing in a subject by administering a substituted tetracycline compound of formula (I). Moreover one of skill in the art would not be motivated by the claims in the '635 patent to develop methods of treating a DMTR associated with splicing in a subject by administering a substituted tetracycline compound. Accordingly, claims 1 and 36-47 are not obvious in view of claims 23-26 of the '635 patent, and therefore, Applicants respectfully request reconsideration and withdrawal of this rejection.

*U.S. Patent No. 6,833,365*

Claims 1, 8, 11 and 36-47 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 20-26 and 33 of U.S. Patent No. 6,833,365 (hereinafter "the '365 patent").

With regard to claims 8 and 11, Applicants respectfully submit that this rejection is moot in view of the cancellation of these claims. With regard to claims 1 and 36-47, Applicants respectfully traverse.

As amended, claims 1 and 36-47 are ***directed to methods for treating a DMTR associated with splicing in a subject*** by administering to the subject an effective amount of a substituted tetracycline compound of formula I.

In contrast, claims 20-26 and 33 of the '365 patent are ***directed to methods of treating a Cryptosporidium parvum related disorder*** in a subject by administering to the subject a substituted tetracycline compound.

Applicants respectfully submit that claims 20-26 and 33 of the '365 patent fail to teach or suggest the currently claimed methods of treating a DMTR associated with splicing in a subject by administering a substituted tetracycline compound of formula (I). Moreover one of skill in the art would not be motivated by the claims in the '365 patent to develop methods of treating a DMTR associated with splicing in a subject by administering a substituted tetracycline compound.

Accordingly, claims 1 and 36-47 are not obvious in view of claims 20-26 and 33 of the '365 patent, and therefore, Applicants respectfully request reconsideration and withdrawal of this rejection.

*U.S. Patent No. 6,846,939*

Claims 1, 8, 11 and 36-47 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 21-24 of U.S. Patent No. 6,846,939 (hereinafter "the '939 patent").

With regard to claims 8 and 11, Applicants respectfully submit that this rejection is moot in view of the cancellation of these claims. With regard to claims 1 and 36-47, Applicants respectfully traverse.

As amended, claims 1 and 36-47 are ***directed to methods for treating a DMTR associated with splicing in a subject*** by administering to the subject an effective amount of a substituted tetracycline compound of formula I.

In contrast, claims 21-24 of the '939 patent are ***directed to methods of treating a tetracycline responsive state (e.g., a bacterial infection associated with E. coli, S. aureus or E. faecalis)*** in a subject by administering to the subject a substituted minocycline compound.

Applicants respectfully submit that claims 21-25 of the '939 patent fail to teach or suggest the currently claimed methods of treating a DMTR associated with splicing in a subject by administering a substituted tetracycline compound of formula (I). Moreover one of skill in the art would not be motivated by the claims in the '939 patent to develop methods of treating a DMTR associated with splicing in a subject by administering a substituted tetracycline compound. Accordingly, claims 1 and 36-47 are not obvious in view of claims 21-24 of the '939 patent, and therefore, Applicants respectfully request reconsideration and withdrawal of this rejection.

*U.S. Patent No. 6,849,615*

Claims 1, 8, 11 and 36-47 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 6-10 of U.S. Patent No. 6,849,615 (hereinafter "the '615 patent").

With regard to claims 8 and 11, Applicants respectfully submit that this rejection is moot in view of the cancellation of these claims. With regard to claims 1 and 36-47, Applicants respectfully traverse.

As amended, claims 1 and 36-47 are *directed to methods for treating a DMTR associated with splicing in a subject* by administering to the subject an effective amount of a substituted tetracycline compound of formula I.

In contrast, claims 6-10 of the '615 patent are *directed to methods of treating a tetracycline responsive state (e.g., a bacterial infection associated with E. coli, S. aureus or E. faecalis)* in a subject by administering to the subject a 13-substituted methacycline compound.

Applicants respectfully submit that claims 6-10 of the '615 patent fail to teach or suggest the currently claimed methods of treating a DMTR associated with splicing in a subject by administering a substituted tetracycline compound of formula (I). Moreover one of skill in the art would not be motivated by the claims in the '615 patent to develop methods of treating a DMTR associated with splicing in a subject by administering a substituted tetracycline compound. Accordingly, claims 1 and 36-47 are not obvious in view of claims 6-10 of the '615 patent, and therefore, Applicants respectfully request reconsideration and withdrawal of this rejection.

*U.S. Patent No. 7,045,507*

Claims 1, 8, 11 and 36-47 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-14, 22-55, 62-65 and 75 of U.S. Patent No. 7,045,507 (hereinafter "the '507 patent").

With regard to claims 8 and 11, Applicants respectfully submit that this rejection is moot in view of the cancellation of these claims. With regard to claims 1 and 36-47, Applicants respectfully traverse.

As amended, claims 1 and 36-47 are *directed to methods for treating a DMTR associated with splicing in a subject* by administering to the subject an effective amount of a substituted tetracycline compound of formula I.

In contrast, claims 1-14, 22-55, 62-65 and 75 of the '507 patent are *directed to methods for increasing the antifungal activity of an antifungal agent and treating a fungal associated disorder* in a subject by administering to the subject a substituted tetracycline compound.

Applicants respectfully submit that claims 1-14, 22-55, 62-65 and 75 of the '507 patent fail to teach or suggest the currently claimed methods of treating a DMTR associated with splicing in a subject by administering a substituted tetracycline compound of formula (I). Moreover one of skill in the art would not be motivated by the claims in the '507 patent to develop methods of treating a DMTR associated with splicing in a subject by administering a substituted tetracycline compound. Accordingly, claims 1 and 36-47 are not obvious in view of claims 1-14, 22-55, 62-65 and 75 of the



'507 patent, and therefore, Applicants respectfully request reconsideration and withdrawal of this rejection.

*U.S. Patent No. 7,094,806*

Claims 1, 8, 11 and 36-47 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 7-11 of U.S. Patent No. 7,094,806 (hereinafter "the '806 patent").

With regard to claims 8 and 11, Applicants respectfully submit that this rejection is moot in view of the cancellation of these claims. With regard to claims 1 and 36-47, Applicants respectfully traverse.

As amended, claims 1 and 36-47 are ***directed to methods for treating a DMTR associated with splicing in a subject*** by administering to the subject an effective amount of a substituted tetracycline compound of formula I.

In contrast, claims 7-11 of the '806 patent are ***directed to methods of treating a tetracycline responsive state (e.g., a bacterial infection associated with E. coli, S. aureus or E. faecalis)*** in a mammal by administering to the mammal a 7, 8 and 9-substituted tetracycline compound.

Applicants respectfully submit that claims 7-11 of the '806 patent fail to teach or suggest the currently claimed methods of treating a DMTR associated with splicing in a subject by administering a substituted tetracycline compound of formula (I). Moreover one of skill in the art would not be motivated by the claims in the '806 patent to develop methods of treating a DMTR associated with splicing in a subject by administering a substituted tetracycline compound. Accordingly, claims 1 and 36-47 are not obvious in view of claims 7-11 of the '806 patent, and therefore, Applicants respectfully request reconsideration and withdrawal of this rejection.

*U.S. Patent No. 7,202,235*

Claims 1, 8, 11 and 36-47 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-27, 34-46 and 49 of U.S. Patent No. 7,202,235 (hereinafter "the '235 patent").

With regard to claims 8 and 11, Applicants respectfully submit that this rejection is moot in view of the cancellation of these claims. With regard to claims 1 and 36-47, Applicants respectfully traverse.

As amended, claims 1 and 36-47 are *directed to methods for treating a DMTR associated with splicing in a subject* by administering to the subject an effective amount of a substituted tetracycline compound of formula I.

In contrast, claims 1-27, 34-46 and 49 of the '235 patent are *directed to methods of controlling Cryptosporidium parvum and treating a Cryptosporidium parvum related disorder* in a mammal by administering to the mammal a 7, 8 and 9-substituted tetracycline compound.

Applicants respectfully submit that claims 1-27, 34-46 and 49 of the '235 patent fail to teach or suggest the currently claimed methods of treating a DMTR associated with splicing in a subject by administering a substituted tetracycline compound of formula (I). Moreover one of skill in the art would not be motivated by the claims in the '235 patent to develop methods of treating a DMTR associated with splicing in a subject by administering a substituted tetracycline compound. Accordingly, claims 1 and 36-47 are not obvious in view of claims 1-27, 34-46 and 49 of the '235 patent, and therefore, Applicants respectfully request reconsideration and withdrawal of this rejection.

***Provisional Rejection of Claims 1, 8, 11 and 36-47 on the Ground of Nonstatutory Obviousness-type Double Patenting***

Claims 1, 8, 11 and 36-47 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims of copending Application Nos. 10/692,563; 10/752,378; 10/786,881 and 10/943,571. Specifically, the Examiner asserts that "[a]lthough the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims represent a genus of claims in each of copending Application Nos. 10/692,563; 10/752,378; 10/786,881 and 10/943,571."

With regard to claims 8 and 11, Applicants respectfully submit that this rejection is moot in view of the cancellation of these claims.

With regard to claim 1 and 36-47, Applicants respectfully submit, while in no way admitting that the present claims are obvious over the claims of co-pending U.S. Patent Application Nos. 10/692,563; 10/752,378; 10/786,881 and 10/943,571, Applicants will consider submitting terminal disclaimer in compliance with 37 C.F.R. 1.321(b) and (c) in Application Nos. 10/692,563; 10/752,378; 10/786,881 and 10/943,571, if appropriate, which will obviate the rejection.

***Rejection of Claims 1-6, 8, 10, 11, 36-47, 54 and 57 under 35 U.S.C. §112, first paragraph***

Claims 1-6, 8, 10, 11, 36-47, 54 and 57 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. Specifically, the Examiner asserts that “it must be considered that the skilled artisan would have to conduct undue and excessive experimentation in order to practice the claimed invention.”

With regard to claims 2-6, 8, 10 and 11, Applicants respectfully submit that this rejection is moot in view of the cancellation of these claims.

With regard to claim 1, 36-47, 54 and 57, Applicants respectfully traverse. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is “undue.” These factors include, but are not limited to: (A) the breadth of the claims; (B) the nature of the invention; (C) the state of the prior art; (D) the level of one of ordinary skill; (E) the level of predictability in the art; (F) the amount of direction provided by the inventor; (G) the existence of working examples; and (H) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. The determination that “undue experimentation” would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations. In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404.

As described above, amended claim 1 and its dependent claims are directed to methods for treating a DMTR associated with splicing in a subject by administering to the subject an effective amount of a substituted tetracycline compound of formula I. Further, Applicants respectfully submit that the relative skill of those skilled in the art in relation to the subject matter is high. With regard to the amount of direction provided by Applicants and the existence of working examples, Applicants respectfully direct the Examiner’s attention to the general synthetic methods described in the specification and to the Examples, which describe the synthesis of representative examples of substituted tetracycline compounds. Additionally, Applicants respectfully direct the Examiner’s attention to page 6, line 24 through page 7, line 20 of the specification, which discloses assays for measuring splicing and spliced forms of mRNA, as well as references which provide guidance for measuring splicing. Moreover, DMTRs associated with splicing are disclosed on page 9, lines 8-22 of the specification and further references are listed which provide guidance for determining DMTRs associated with splicing. Accordingly, one skilled in the art in possession of the specification at the time it was filed would have been able to practice the invention with no more than routine experimentation. Additionally, the fact that experimentation may be complex does not

necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (*Int'l Trade Comm'n* 1983), *aff'd. sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). Moreover, it is not necessary to specify the dosage or method of use if it is known to one skilled in the art that such information could be obtained without undue experimentation. If one skilled in the art, based on knowledge of compounds having similar physiological or biological activity, would be able to discern an appropriate dosage or method of use without undue experimentation, this would be sufficient to satisfy 35 U.S.C. 112, first paragraph. See MPEP 2164.01(c). Upon weighing these factors, Applicants respectfully submit that a skilled artisan in possession of the specification would be able to make and use the claimed invention without undue experimentation.

Based at least on the foregoing, Applicants respectfully request reconsideration and withdrawal of this rejection of the claims.

***Rejection of Claims 1-6, 8, 10, 11, 36-47, 54 and 57 under 35 U.S.C. §112, first paragraph***

Claims 1-6, 8, 10, 11, 36-47, 54 and 57 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. Specifically, the Examiner asserts that “[t]he skilled artisan would conclude the Applicant’s were not in possession of the claimed invention.”

With regard to claims 2-6, 8, 10 and 11, Applicants respectfully submit that this rejection is moot in view of the cancellation of these claims.

With regard to claim 1, 36-47, 54 and 57 Applicants respectfully traverse. However, to expedite prosecution, Applicants have amended claim 1 to be directed to methods for treating a DMTR associated with splicing in a subject by administering a substituted tetracycline compound of formula I. Accordingly, the Examiner’s rejection of the claims under 35 U.S.C. § 112, first paragraph, does not pertain to the currently pending claims, because the currently claimed subject matter is described in the specification in a manner which would enable one of ordinary skill in the art to use the invention for at least the following reasons.

As described above, the specification, at least at page 6, line 24 through page 7, line 20 discloses assays for measuring splicing and spliced forms of mRNA, as well as references which provide guidance for measuring splicing. Moreover, DMTRs associated with splicing are disclosed at least at page 9, lines 8-22 of the specification and further references are listed therewith which provides guidance for determining DMTRs associated with splicing. Further, at least at page 80,

line 35 through page 86, line 5 and Example 1 provide synthetic methods for the synthesis of representative substituted tetracycline compounds of the invention for use in treating a DMTR associated with splicing.

Accordingly, Applicants respectfully submit that the specification describes the claimed invention in sufficient detail that a skilled artisan would conclude that Applicants had possession of the claimed invention at the time the application was filed. Based at least on the foregoing, Applicants respectfully request reconsideration and withdrawal of this rejection.

***Rejection of Claims 1, 2, 8, 10, 11 and 36-38 under 35 U.S.C. §102(b)***

Claims 1, 2, 8, 10, 11 and 36-38 are rejected under 35 U.S.C. §102(b) as being taught by Yrjanheikki *et al.* ("Tetracyclines Inhibit Microglial Activation and are Neuroprotective in Global Brain Ischemia," *PNAS* (1998) 95:15769-15574). Specifically, the Examiner asserts that "Yrjanheikki teaches the claimed invention."

With regard to claims 2, 8, 10 and 11, Applicants respectfully submit that this rejection is moot in view of the cancellation of these claims.

With regard to claims 1 and 36-38, Applicants respectfully traverse. As described above, claim 1 and its dependent claims are ***directed to methods for treating a DMTR associated with splicing in a subject*** by administering to the subject an effective amount of a substituted tetracycline compound of formula I.

In contrast, Yrjanheikki discloses the use of doxycycline and minocycline ***as protective agents for ischemic stroke***. Yrjanheikki also discloses that minocycline prevents microglial activation without affecting astrogliosis and that minocycline inhibits induction of interleukin-1 $\beta$ -converting enzyme mRNA, decreases induction of iNOS mRNA and prevents nitric oxide synthase protein expression. However, Yrjanheikki fails to teach or suggest the substituted tetracycline compounds of formula I for treating a DMTR associated with splicing in a subject. Applicants respectfully submit that the induction of ICE mRNA, downregulation of iNOS and the prevention of NOS protein expression by minocycline and the protection of neurons against stroke by minocycline and doxycycline does not anticipate the use of a substituted tetracycline compound of formula I for the treatment of a DMTR associated with splicing. Accordingly, Applicants respectfully submit that Yrjanheikki does not anticipate the claimed invention.

Based at least on the foregoing, Applicants respectfully request reconsideration and withdrawal of this rejection.

***Rejection of Claims 1, 8, 11 and 36-47 under 35 U.S.C. §102(e)***

Claims 1, 8, 11 and 36-47 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent Nos. 6,500,812; 6,624,168; 6,642,270; 6,683,068; 6,818,634; 6,818,635; 6,846,939; 6,849,615; 7,045,507; 6,094,806 and 7,202,235; and U.S. Patent Publication Nos. 20040242548; 20040266740; 20050026876 and 20050070510. Applicants respectfully traverse this rejection as set forth below.

***U.S. Patent No. 6,500,812***

Claims 1, 8, 11 and 36-47 are rejected under 35 U.S.C. §102(e) as being anticipated by U.S. Patent No. 6,500,812 (hereinafter “the ‘812 patent”). Specifically, the Examiner asserts that the ‘812 patent “teaches a method of treating a tetracycline response state in a mammal, comprising the administration of a tetracycline compound, such that the tetracycline state is treated.”

With regard to claims 8 and 11, Applicants respectfully submit that this rejection is moot in view of the cancellation of these claims. With regard to claims 1 and 36-47, Applicants respectfully traverse.

As amended, claims 1 and 36-47 are ***directed to methods for treating a DMTR associated with splicing in a subject*** by administering to the subject an effective amount of a substituted tetracycline compound of formula I.

In contrast, the ‘812 patent discloses ***methods for treating a tetracycline responsive state*** in a mammal by administering to the mammal a 13-substituted methacycline compound.

Applicants respectfully submit that the ‘812 patent fails to teach or suggest the currently claimed methods of treating a DMTR associated with splicing in a subject by administering a substituted tetracycline compound of formula (I). Accordingly, claims 1 and 36-47 are not anticipated by the ‘812 patent, and therefore, Applicants respectfully request reconsideration and withdrawal of this rejection.

***U.S. Patent No. 6,624,168***

Claims 1, 8, 11 and 36-47 are rejected under 35 U.S.C. §102(e) as being anticipated by U.S. Patent No. 6,624,168 (hereinafter “the ‘168 patent”). Specifically, the Examiner asserts that the ‘168 patent “teaches a method of treating a tetracycline response state in a mammal, comprising the administration of a tetracycline compound, such that the tetracycline state is treated.”

With regard to claims 8 and 11, Applicants respectfully submit that this rejection is moot in view of the cancellation of these claims. With regard to claims 1 and 36-47, Applicants respectfully traverse.

As amended, claims 1 and 36-47 are ***directed to methods for treating a DMTR associated with splicing in a subject*** by administering to the subject an effective amount of a substituted tetracycline compound of formula I.

In contrast, the '168 patent discloses ***methods of treating a tetracycline responsive state (e.g., a bacterial infection associated with E. coli, S. aureus or E. faecalis)*** in a mammal by administering to the mammal a 7, 8 and 9-substituted tetracycline compound.

Applicants respectfully submit that the '168 patent fails to teach or suggest the currently claimed methods of treating a DMTR associated with splicing in a subject by administering a substituted tetracycline compound of formula (I). Accordingly, claims 1 and 36-47 are not anticipated by '168 patent, and therefore, Applicants respectfully request reconsideration and withdrawal of this rejection.

***U.S. Patent No. 6,642,270***

Claims 1, 8, 11 and 36-47 are rejected under 35 U.S.C. §102(e) as being anticipated by U.S. Patent No. 6,642,270 (hereinafter "the '270 patent"). Specifically, the Examiner asserts that the '270 patent "teaches a method of treating a tetracycline response state in a mammal, comprising the administration of a tetracycline compound, such that the tetracycline state is treated."

With regard to claims 8 and 11, Applicants respectfully submit that this rejection is moot in view of the cancellation of these claims. With regard to claims 1 and 36-47, Applicants respectfully traverse.

As amended, claims 1 and 36-47 are ***directed to methods for treating a DMTR associated with splicing in a subject*** by administering to the subject an effective amount of a substituted tetracycline compound of formula I.

In contrast, the '270 patent discloses ***methods of treating a tetracycline responsive state (e.g., a bacterial infection associated with E. coli, S. aureus or E. faecalis)*** in a mammal by administering to the mammal a 7-substituted fused ring tetracycline compound.

Applicants respectfully submit that the '270 patent fails to teach or suggest the currently claimed methods of treating a DMTR associated with splicing in a subject by administering a substituted tetracycline compound of formula (I). Accordingly, claims 1 and 36-47 are not

anticipated by the '270 patent, and therefore, Applicants respectfully request reconsideration and withdrawal of this rejection.

*U.S. Patent No. 6,683,068*

Claims 1, 8, 11 and 36-47 are rejected under 35 U.S.C. §102(e) as being anticipated by U.S. Patent No. 6,683,068 (hereinafter "the '068 patent"). Specifically, the Examiner asserts that the '068 patent "teaches a method of treating a bacterial infection in a human, comprising the administration of a tetracycline compound, such that the bacterial infection is treated."

With regard to claims 8 and 11, Applicants respectfully submit that this rejection is moot in view of the cancellation of these claims. With regard to claims 1 and 36-47, Applicants respectfully traverse.

As amended, claims 1 and 36-47 are ***directed to methods for treating a DMTR associated with splicing in a subject*** by administering to the subject an effective amount of a substituted tetracycline compound of formula I.

In contrast, the '068 patent discloses ***methods of treating a tetracycline responsive state (e.g., a bacterial infection associated with E. coli, S. aureus or E. faecalis)*** in a subject by administering to the subject a 7,9-substituted tetracycline compound.

Applicants respectfully submit that the '068 patent fails to teach or suggest the currently claimed methods of treating a DMTR associated with splicing in a subject by administering a substituted tetracycline compound of formula (I). Moreover one of skill in the art would not be motivated by the claims in the '068 patent to develop methods of treating a viral disorder in a subject by administering a substituted tetracycline compound. Accordingly, claims 1 and 36-47 are not anticipated by the '068 patent, and therefore, Applicants respectfully request reconsideration and withdrawal of this rejection.

*U.S. Patent No. 6,818,634*

Claims 1, 8, 11 and 36-47 are rejected under 35 U.S.C. §102(e) as being anticipated by U.S. Patent No. 6,818,634 (hereinafter "the '634 patent"). Specifically, the Examiner asserts that the '634 patent "teaches a method of treating a tetracycline response state in a human, comprising the administration of a tetracycline compound, such that the tetracycline response is treated."

With regard to claims 8 and 11, Applicants respectfully submit that this rejection is moot in view of the cancellation of these claims. With regard to claims 1 and 36-47, Applicants respectfully traverse.



As amended, claims 1 and 36-47 are *directed to methods for treating a DMTR associated with splicing in a subject* by administering to the subject an effective amount of a substituted tetracycline compound of formula I.

In contrast, the '634 patent discloses *methods of treating a tetracycline responsive state (e.g., a bacterial infection associated with E. coli, S. aureus, E. faecalis or E. hirae)* in a subject by administering to the subject a 7-hydrogen, dialkylamino or heteroaryl-amino substituted tetracycline compound.

Applicants respectfully submit that the '634 patent fails to teach or suggest the currently claimed methods of treating a DMTR associated with splicing in a subject by administering a substituted tetracycline compound of formula (I). Accordingly, claims 1 and 36-47 are not anticipated by the '634 patent, and therefore, Applicants respectfully request reconsideration and withdrawal of this rejection.

*U.S. Patent No. 6,818,635*

Claims 1, 8, 11 and 36-47 are rejected under 35 U.S.C. §102(e) as being anticipated by U.S. Patent No. 6,818,635 (hereinafter "the '635 patent"). Specifically, the Examiner asserts that the '635 patent "teaches a method of treating a *Cryptosporidium parvum* disorder in a human, comprising the administration of a tetracycline compound, such that the *Cryptosporidium parvum* disorder is treated."

With regard to claims 8 and 11, Applicants respectfully submit that this rejection is moot in view of the cancellation of these claims. With regard to claims 1 and 36-47, Applicants respectfully traverse.

As amended, claims 1 and 36-47 are *directed to methods for treating a DMTR associated with splicing in a subject* by administering to the subject an effective amount of a substituted tetracycline compound of formula I.

In contrast, the '635 patent discloses *methods of treating a tetracycline responsive state (e.g., a bacterial infection associated with E. coli, S. aureus or E. faecalis)* in a subject by administering to the subject a 7-alkynyl substituted tetracycline.

Applicants respectfully submit that the '635 patent fails to teach or suggest the currently claimed methods of treating a DMTR associated with splicing in a subject by administering a substituted tetracycline compound of formula (I). Accordingly, claims 1 and 36-47 are not anticipated by the '635 patent, and therefore, Applicants respectfully request reconsideration and withdrawal of this rejection.

*U.S. Patent No. 6,846,939*

Claims 1, 8, 11 and 36-47 are rejected under 35 U.S.C. §102(e) as being anticipated by U.S. Patent No. 6,846,939 (hereinafter “the ‘939 patent”).

With regard to claims 8 and 11, Applicants respectfully submit that this rejection is moot in view of the cancellation of these claims. With regard to claims 1 and 36-47, Applicants respectfully traverse.

As amended, claims 1 and 36-47 are ***directed to methods for treating a DMTR associated with splicing in a subject*** by administering to the subject an effective amount of a substituted tetracycline compound of formula I.

In contrast, the ‘939 patent discloses ***methods of treating a tetracycline responsive state (e.g., a bacterial infection associated with E. coli, S. aureus or E. faecalis)*** in a subject by administering to the subject a substituted minocycline compound.

Applicants respectfully submit that the ‘939 patent fails to teach or suggest the currently claimed methods of treating a DMTR associated with splicing in a subject by administering a substituted tetracycline compound of formula (I). Accordingly, claims 1 and 36-47 are not anticipated by the ‘939 patent, and therefore, Applicants respectfully request reconsideration and withdrawal of this rejection.

*U.S. Patent No. 6,849,615*

Claims 1, 8, 11 and 36-47 are rejected under 35 U.S.C. §102(e) as being anticipated by U.S. Patent No. 6,849,615 (hereinafter “the ‘615 patent”). Specifically, the Examiner asserts that the ‘615 patent “teaches a method of treating a tetracycline response state in a human, comprising the administration of a tetracycline compound, such that the tetracycline state is treated.”

With regard to claims 8 and 11, Applicants respectfully submit that this rejection is moot in view of the cancellation of these claims. With regard to claims 1 and 36-47, Applicants respectfully traverse.

As amended, claims 1 and 36-47 are ***directed to methods for treating a DMTR associated with splicing in a subject*** by administering to the subject an effective amount of a substituted tetracycline compound of formula I.

In contrast, the ‘615 patent disclose ***methods of treating a tetracycline responsive state (e.g., a bacterial infection associated with E. coli, S. aureus or E. faecalis)*** in a subject by administering to the subject a 13-substituted methacycline compound.

Applicants respectfully submit that the '615 patent fails to teach or suggest the currently claimed methods of treating a DMTR associated state in a subject by administering a substituted tetracycline compound of formula (I). Accordingly, claims 1 and 36-47 are anticipated by the '615 patent, and therefore, Applicants respectfully request reconsideration and withdrawal of this rejection.

*U.S. Patent No. 7,045,507*

Claims 1, 8, 11 and 36-47 are rejected under 35 U.S.C. §102(e) as being anticipated by U.S. Patent No. 7,045,507 (hereinafter "the '507 patent"). Specifically the Examiner asserts that the '507 patent "teaches a method of treating a fungal infection, comprising the administration of a tetracycline compound, such that the fungal infection is treated."

With regard to claims 8 and 11, Applicants respectfully submit that this rejection is moot in view of the cancellation of these claims. With regard to claims 1 and 36-47, Applicants respectfully traverse.

As amended, claims 1 and 36-47 are ***directed to methods for treating a DMTR associated state in a subject*** by administering to the subject an effective amount of a substituted tetracycline compound of formula I.

In contrast, the '507 patent disclose ***methods for increasing the antifungal activity of an antifungal agent and treating a fungal associated disorder*** in a subject by administering to the subject a substituted tetracycline compound.

Applicants respectfully submit that the '507 patent fails to teach or suggest the currently claimed methods of treating a DMTR associated with splicing in a subject by administering a substituted tetracycline compound of formula (I). Accordingly, claims 1 and 36-47 are not anticipated by the '507 patent, and therefore, Applicants respectfully request reconsideration and withdrawal of this rejection.

*U.S. Patent No. 7,094,806*

Claims 1, 8, 11 and 36-47 are rejected under 35 U.S.C. §102(e) as being anticipated by U.S. Patent No. 7,094,806 (hereinafter "the '806 patent"). Specifically, the Examiner asserts that the '806 patent "teaches a method of treating a tetracycline response state in a human, comprising the administration of a tetracycline compound, such that the tetracycline state is treated."

With regard to claims 8 and 11, Applicants respectfully submit that this rejection is moot in view of the cancellation of these claims. With regard to claims 1 and 36-47, Applicants respectfully traverse.

As amended, claims 1 and 36-47 are ***directed to methods for treating a DMTR associated with splicing in a subject*** by administering to the subject an effective amount of a substituted tetracycline compound of formula I.

In contrast, '806 patent discloses ***methods of treating a tetracycline responsive state (e.g., a bacterial infection associated with E. coli, S. aureus or E. faecalis)*** in a mammal by administering to the mammal a 7, 8 and 9-substituted tetracycline compound.

Applicants respectfully submit that the '806 patent fail to teach or suggest the currently claimed methods of treating a DMTR associated with splicing in a subject by administering a substituted tetracycline compound of formula (I). Accordingly, claims 1 and 36-47 are not anticipated by the '806 patent, and therefore, Applicants respectfully request reconsideration and withdrawal of this rejection.

*U.S. Patent No. 7,202,235*

Claims 1, 8, 11 and 36-47 are rejected under 35 U.S.C. §102(e) as being anticipated by U.S. Patent No. 7,202,235 (hereinafter "the '235 patent"). Specifically, the Examiner asserts that the '235 patent "teaches a method of treating a *Cryptosporidium parvum* disorder in a human, comprising the administration of a tetracycline compound, such that the *Cryptosporidium parvum* disorder is treated."

With regard to claims 8 and 11, Applicants respectfully submit that this rejection is moot in view of the cancellation of these claims. With regard to claims 1 and 36-47, Applicants respectfully traverse.

As amended, claims 1 and 36-47 are ***directed to methods for treating a DMTR associated with splicing in a subject*** by administering to the subject an effective amount of a substituted tetracycline compound of formula I.

In contrast the '235 patent disclose ***methods of controlling Cryptosporidium parvum and treating a Cryptosporidium parvum related disorder*** in a mammal by administering to the mammal a 7, 8 and 9-substituted tetracycline compound.

Applicants respectfully submit that the '235 patent fails to teach or suggest the currently claimed methods of treating a DMTR associated with splicing in a subject by administering a substituted tetracycline compound of formula (I). Accordingly, claims 1 and 36-47 are not

anticipated by the '235 patent, and therefore, Applicants respectfully request reconsideration and withdrawal of this rejection.

*U.S. Patent Publication No. 20040242548*

Claims 1, 8, 11 and 36-47 are rejected under 35 U.S.C. §102(e) as being anticipated by U.S. Patent Publication No. 20040242548 (hereinafter "the '548 application"). Specifically, the Examiner asserts that the '548 application "teaches a method of treating malaria in a subject, comprising the administration of a tetracycline compound, such that malaria is treated."

With regard to claims 8 and 11, Applicants respectfully submit that this rejection is moot in view of the cancellation of these claims. With regard to claims 1 and 36-47, Applicants respectfully traverse.

As amended, claims 1 and 36-47 are ***directed to methods for treating a DMTR associated with splicing in a subject*** by administering to the subject an effective amount of a substituted tetracycline compound of formula I.

In contrast the '548 application discloses ***methods of treating malaria*** in a subject by administering to the subject a substituted tetracycline compound.

Applicants respectfully submit that the '548 application fails to teach or suggest the currently claimed methods of treating a DMTR associated with splicing in a subject by administering a substituted tetracycline compound of formula (I). Accordingly, claims 1 and 36-47 are not anticipated by the '548 application, and therefore, Applicants respectfully request reconsideration and withdrawal of this rejection.

*U.S. Patent Publication No. 20040266740*

Claims 1, 8, 11 and 36-47 are rejected under 35 U.S.C. §102(e) as being anticipated by U.S. Patent Publication No. 20040266740 (hereinafter "the 740 application"). Specifically, the Examiner asserts that the '740 application "teaches a method of treating a tetracycline response state in a human, comprising the administration of a tetracycline compound, such that the tetracycline state is treated."

With regard to claims 8 and 11, Applicants respectfully submit that this rejection is moot in view of the cancellation of these claims. With regard to claims 1 and 36-47, Applicants respectfully traverse.

As amended, claims 1 and 36-47 are ***directed to methods for treating a DMTR associated with splicing in a subject*** by administering to the subject an effective amount of a substituted tetracycline compound of formula I.

In contrast, the '740 application discloses ***methods of treating a tetracycline responsive state (e.g., a bacterial infection associated with E. coli, S. aureus or E. faecalis)*** in a subject by administering to the subject a substituted tetracycline compound.

Applicants respectfully submit that the '740 application fails to teach or suggest the currently claimed methods of treating a DMTR associated with splicing in a subject by administering a substituted tetracycline compound of formula (I). Accordingly, claims 1 and 36-47 are not anticipated by the '740 application, and therefore, Applicants respectfully request reconsideration and withdrawal of this rejection.

*U.S. Patent Publication No. 20050026876*

Claims 1, 8, 11 and 36-47 are rejected under 35 U.S.C. §102(e) as being anticipated by U.S. Patent Publication No. 20050026876 (hereinafter "the '876 application"). Specifically, the Examiner asserts that the '876 application "teaches a method of treating a tetracycline response state in a human, comprising the administration of a tetracycline compound, such that the tetracycline state is treated."

With regard to claims 8 and 11, Applicants respectfully submit that this rejection is moot in view of the cancellation of these claims. With regard to claims 1 and 36-47, Applicants respectfully traverse.

As amended, claims 1 and 36-47 are ***directed to methods for treating a DMTR associated with splicing in a subject*** by administering to the subject an effective amount of a substituted tetracycline compound of formula I.

In contrast, the '876 application discloses ***methods of treating a tetracycline responsive state (e.g., a bacterial infection associated with E. coli, S. aureus or E. faecalis)*** in a subject by administering to the subject a substituted tetracycline compound.

Applicants respectfully submit that the '876 application fails to teach or suggest the currently claimed methods of treating a DMTR associated with splicing in a subject by administering a substituted tetracycline compound of formula (I). Accordingly, claims 1 and 36-47 are not anticipated by the '876 application, and therefore, Applicants respectfully request reconsideration and withdrawal of this rejection.

*U.S. Patent Publication No. 20050070510*

Claims 1, 8, 11 and 36-47 are rejected under 35 U.S.C. §102(e) as being anticipated by U.S. Patent Publication No. 20050070510 (hereinafter “the ‘510 application”). Specifically, the Examiner asserts that the ‘510 application “teaches a method of treating a fungus and a fungal infection in a human, comprising the administration of a tetracycline compound, such that the tetracycline state is treated.”

With regard to claims 8 and 11, Applicants respectfully submit that this rejection is moot in view of the cancellation of these claims. With regard to claims 1 and 36-47, Applicants respectfully traverse.

As amended, claims 1 and 36-47 are ***directed to methods for treating a DMTR associated with splicing in a subject*** by administering to the subject an effective amount of a substituted tetracycline compound of formula I.

In contrast, the ‘510 application discloses ***methods of treating a fungal infection*** in a subject by administering to the subject a substituted tetracycline compound.

Applicants respectfully submit that the ‘510 application fails to teach or suggest the currently claimed methods of treating a DMTR associated with splicing in a subject by administering a substituted tetracycline compound of formula (I). Accordingly, claims 1 and 36-47 are not anticipated by the ‘510 application, and therefore, Applicants respectfully request reconsideration and withdrawal of this rejection.

Application No.: 10/692,764  
Examiner: K.A. Makar

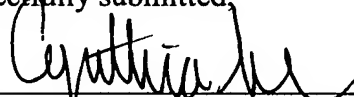
Docket No.: PAZ-205CP  
Group Art Unit: 1636

**SUMMARY**

It is respectfully submitted that this application is in condition for allowance. If there are any remaining issues or the Examiner believes that a telephone conference with Applicants' Attorney would be helpful in expediting prosecution of this application, the Examiner is invited to call the undersigned at (617) 227-7400.

Dated: November 5, 2007

Respectfully submitted,

By 

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